REMARKS

Applicants respectfully request entry of the amendment and reconsideration of the claims.

Claims 2, and 22-29 have been canceled without prejudice. Applicants reserve the right to pursue the subject matter of these claims in one or more continuation applications. Applicants note that claims 7-11, 15-18 and 23-26 are withdrawn and can be rejoined upon notice of allowable subject matter of linking claims 1-6, 14 and 22. Applicants request clarification concerning claim 11. Applicants note that the claim 11 is listed as withdrawn but is in fact one of the claims in the elected group of claims.

Claims 1, 30 and 32 have been amended to further clarify the claimed invention. Claims 39-44 are newly presented. After entry of the amendment, claims 1, 3-21, and 30-44 will be pending.

Applicants submit the amendment is supported throughout the specification, including for example at page 23, line 37 to page 25, line 15, page 25, lines 24-27, and Example 7, and does not raise any issues of new matter.

Restriction Requirement

Applicants affirm the election without traverse to prosecute the invention of Group II, claims 11-13, 19-21, 27-29, and 36-38, made during a telephone conversation with the Examiner on June 20, 2006. Applicants acknowledge the withdrawal of claims 7-10, 15-18, and 23-26 from further consideration as drawn to non-elected inventions. Applicants note claims 1-6, 14, 22 and 30-35 are linking claims. Upon notice of allowance of the linking claims, the withdrawn claims 7-10, 15-18 and 23-26 may be rejoined and examined.

Claim Objections

The Examiner objected to claims 32-34 under 37 C.F.R. § 1.75(b) as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. Claims 32 has been amended to depend from claim 30. Withdrawal of the objection is respectfully requested.

Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claim 31 under 35 U.S.C. § 112, first paragraph as allegedly lacking written description. This is a new matter rejection. The Office Action asserts claim 31 includes new matter because the conditions recited in the claim are not associated in the specification with cerebral edema. Applicants respectfully traverse the rejection.

As an initial matter, Applicants note there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. *See* Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, first paragraph "Written Description Requirement" IIA. Furthermore, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by reduction to practice, by disclosure of relevant identifying characteristics such as structure, physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of these characteristics. *MPEP 2163 II. A.3.(a)ii)*. When the above factors are carefully weighed, the specification clearly describes the claimed subject matter in a manner reasonably conveying to one of skill in the art that Applicants had possession of the claimed invention.

The specification provides that CNS edema is typically characterized by an increase in brain volume and intracranial pressure. The increase in brain volume can be, for example, the result of increased cerebral volume and/or increased tissue water content. See specification at page 23, lines 38-39 and page 24, lines 1-3. Moreover, the specification at page 24 provides that the conditions are associated at least with an increase in tissue water content, which can result in or contribute to CNS edema. See the specification for example at page 23, lines 32-36 and page 24, lines 11-17. The specification directly refers to edema due to conditions that can involve the central nervous system such as cerebral malaria, trauma (such as head injury), stroke, encephalitis, meningitis, hypoxia, multiple sclerosis, hemorrhage, viral infection, ischemia, encephalopathy, glutamate toxicity, birth asphyxia, radiation. See the specification at page 24, lines 11-17.

In view of the forgoing, Applicants submit claim 31 does not recite any new matter and that the conditions recited in the claim are fully supported by the specification. Withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. § 102

Claim 1 was rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by either Jirousek (U.S. 6,093,740) or Aiello (U.S. 6,114,320). Applicants respectfully traverse the rejection.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *See* MPEP 2131.01, citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). The identical invention must be shown in the same complete detail as is recited by the claims. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Since Jirousek or Aiello do not disclose a method having each and every element of Applicants' claimed methods, Jirousek or Aiello do not anticipate the claims.

The claims as amended are directed to methods of treating CNS edema, wherein the VEGF antagonist inhibits the interaction of hVEGF with a hVEGF receptor. Applicants submit that neither Aiello ('320) nor Jirousek ("740) discloses treatment of CNS edema with a VEGF antagonist. At least for this reason, these references do not anticipate the claims.

Withdrawal of these rejections is respectfully requested.

Claims 1 and 11-13 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Aiello-II (Aiello et al., 1995, *Proceedings of the National Academy of Sciences. USA*, 92:10457-10461) as evidenced by Aiello (*supra*). Applicants respectfully traverse this rejection.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *See* MPEP 2131.01, citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). The identical invention must be shown in the same complete detail as is recited by the claims. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Since Aiello-I and Aiello-II do not disclose a method having each and every element of Applicants' claimed methods, Aiello-I and Aiello-II do not anticipate the claims.

Applicants submit that Aiello-II does not disclose treatment of edema as the reference is directed to treatment of neovascularization. Moreover, neither reference discloses treatment of CNS edema. Thus, for at least this reason, these references do not anticipate the claims.

Withdrawal of the rejection is respectfully requested.

The Examiner rejected claims 1-5, 11-13, 22, and 27-29 under 35 U.S.C. § 102(b) as allegedly being anticipated by Ferrara (WO 94/10202). Claims 2, 22 and 27-29 have been canceled rendering the rejection of these claims moot. Applicants respectfully traverse this rejection.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *See* MPEP 2131.01, citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). The identical invention must be shown in the same complete detail as is recited by the claims. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989).

Applicants' claims are directed to a method of treating a mammal having CNS edema comprising administering to said mammal an effective amount of a hVEGF antagonist, wherein the antagonist inhibits interaction of hVEGF with a hVEGF receptor. Applicants submit that WO 94/10202 does not disclose all of the elements of Applicants' claims.

The Office Action effectively asserts that if the prior art teaches a method that comprises the same steps of administering a pharmaceutical agent as a claimed method, it is not necessary for the prior art to teach a new use of the same pharmaceutical agent. Applicants respectfully disagree.

Ferrara does not anticipate the claimed methods because Applicants' methods are directed to a new use. The claimed methods are not directed to the same use or necessarily the same patient population as the methods taught by Ferrara. Ferrara teaches administering hVEGF antagonists to inhibit tumor growth, which is associated with angiogenesis. See Ferrara at Example 4. In contrast, the claimed methods are directed to administering a hVEGF antagonist to reduce CNS edema, such as cerebral edema, which is associated with an increase in tissue water content. See Specification at Example 7. Accordingly, Applicants respectfully request withdrawal of the rejection.

In addition, Applicants submit that Ferrara does not disclose all of the elements of the claims, including administering an effective amount of a hVEGF antagonist to reduce CNS edema. Applicants submit that at the time of the Ferrara reference, there was contradictory evidence about the role of VEGF in edema as discussed by Dr. Van Bruggen in his Declaration. (copy submitted herewith) There was no evidence of direct causation of edema by VEGF that would lead one of skill in the art to understand that inhibition of VEGF by an antagonist would be useful to reduce CNS edema. As stated in the Declaration of Dr. Van Bruggen submitted in the parent application 09/718,694 (copy enclosed; hereinafter the Declaration), at the time of the filing of the present application the literature presented contradictory evidence concerning VEGF involvement in edema. See Declaration paragraphs 4 to 8. In some studies VEGF expression was more strongly correlated with tumor vascularity than cerebral edema. Berkman et al., 1993, *J. Clin. Invest.*, 91:153-159 at page 157. A more recent study of glioblastomas failed to show a significant correlation between the degree of VEGF and the degree of peritumoral edema. Vaquero et al., 2000, *J. Neuro-Oncology*, 49:49-55 at page 49. Thus, Ferrera et al. does not teach all of the elements of the claims, including that an effective amount of a hVEGF antagonist is useful to reduce CNS edema.

Claim Rejections Under 35 U.S.C. § 103

The Examiner rejected claims 1, 6, 14-21, and 30-38 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ferrara (*supra*) in view of Aiello (*supra*, U.S. Patent 6,114,320). Applicants respectfully traverse the rejection.

To establish *prima facie* obviousness, three basic criteria must be met, namely: 1) suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; 2) a reasonable expectation of success; and 3) the references when combined must teach or suggest all the claim limitations. MPEP §2142. Applicants submit the requirements have not been met, in the least, wherein the combined cited references do not teach or suggest all of the claim limitations, there would be no motivation to combine the references and there would be no reasonable expectation of success of achieving the claimed invention.

Even when the references are combined, they do not disclose all of the elements of Applicants' claims. As discussed previously, the Ferrara et al. reference does not in the least disclose a method of treating CNS edema with an effective amount of a hVEGF antagonist. As discussed previously, at the time of the Ferrara reference, one of skill in the art would not have understood that CNS edema could be treated with a hVEGF antagonist, because there was contradictory evidence about whether VEGF was involved in edema, such as cerebral edema. For example, there was no evidence that VEGF was a direct cause of cerebral edema.

This deficiency is not remedied by Aiello. Aiello is directed to ocular tissue and not to CNS edema. Regardless of whether the reference discloses that hypoxia is associated with an increase in VEGF in the eye, there is no evidence in this reference that similar effects would be observed in the central nervous system or brain. As presented in the Declaration of Dr. Van Bruggen, the evidence concerning VEGF and cerebral edema was contradictory. Moreover, neither Aiello nor Ferrara discusses CNS edema associated with non-neoplastic conditions as indicated in the claims. The general discussion of Aiello regarding the association of hypoxia and VEGF in eye tissue does not make it obvious that every condition that might involve hypoxia may be treatable with a hVEGF antagonist. In fact, the references described by Dr. Van Bruggen indicate that the relationship of VEGF and cerebral edema was not clear.

Thus, Applicants submit even if combined, the references do not teach or suggest all of the claim limitations.

Applicants also submit that there would be no motive to combine the references.

"A rejection cannot be predicated on the mere identification . . . of individual components of the claimed invention." Rather, particular findings must be made as to the reason the skilled artisan, with no known knowledge of the claimed invention, would have selected these components for combination in the manner claimed." *Ecolochem Inc. v. Southern Calif. Edison Co.*, 227 F3d 1361, 1375 (Fed. Cir. 2000). Applicants submit the Examiner is using hindsight reconstruction to piece together pieces of individual references to reject the claims as obvious.

The Examiner has not established a motive to combine these two references. As discussed previously, the Ferrara et al. reference does not disclose a method of treating CNS edema with an effective amount of a hVEGF antagonist. The relationship of VEGF activity and CNS edema was not clear at the time of the Ferrara et al. reference. Ferrara teaches administering

hVEGF antagonists to inhibit tumor growth, which is associated with angiogenesis. The Aiello reference is directed to treating diseases of the eye. There is no teaching or suggestion in the reference that a VEGF antagonist can or should be used to treat CNS edema, such as cerebral edema. Each of these references are directed to treatment of different conditions and, therefore, there would be no motivation to combine these references.

Finally, Applicants submit there would be no reasonable expectation of success that an effective amount of a hVEGF antagonist could reduce the volume of cerebral edema.

As discussed in the Declaration by Dr. Van Bruggen submitted in the parent application 09/718,694 (copy enclosed; hereinafter the Declaration), at the time of the filing of the present application it could not be predicted if VEGF was a causative agent of edema or if an antagonist of VEGF could successfully treat cerebral edema. Dr. Van Bruggen explains that this lack of predictability is because of contradictory experimental observations cited in the literature and lack of direct evidence of causation. See Declaration at paragraphs 3-13.

As explained by Dr. Van Bruggen, at the time of filing the application the literature presented contradictory evidence concerning VEGF involvement in cerebral edema. See Declaration at paragraphs 4 to 8. In some studies, VEGF expression was more strongly correlated with tumor vascularity rather than cerebral edema. See Berkman et al, 1993, *J. Clin. Investigation,* 91: 153-159 at page 157. Hayashi et al. (1998, *J. Cereb. Blood Flow Metab.,* 18:887-895) reported that VEGF itself, when applied topically to the surface of a reperfused rat brain after transient cerebral artery occlusion, reduced ischemic brain damage, infarct volume, and edema formation. A more recent study of glioblastomas failed to show a significant correlation between the degree of VPF and the degree of peritumoral edema. See Vaquero et al., 2000, *J. Neuro-Oncology 49:49-55* at page 49. The authors state that their results suggest that factors other than intratumoral presence of VPF may contribute to the development of peritumoral edema. Vaquero et al., *supra.*

In other studies, such as those of Kalkanis et al., 1996, *J. Neurosurg.* 85:1095-1101 and Strugar et al., 1994, *J. Neurosurg.* 81:560-566, a strong correlation was found between expression of VEGF and edema, but no evidence of direct causation of edema by VEGF was presented. See Declaration at paragraphs 6, 7 and 16. Although it was hypothesized that VEGF

played a role in edema formation, this hypothesis could not be verified without an antagonist effective in an animal model.

At the time of the filing of the above referenced application, one skilled in the art could not predict if VEGF was a causative agent of cerebral edema because of the lack of VEGF antagonists effective in a rodent model for the treatment of cerebral edema. See Declaration at paragraphs 7-9. Because the majority of research studies are performed on rodents, the lack of a suitable pharmacological VEGF antagonist effective in either rat or mouse prevented a clear understanding of the contribution of VEGF in the pathogenesis of stroke and related disorders. See van Bruggen et al., 1999, *J. Clin. Investigation* 104:1613-1629 at page 1613. Those skilled in the art recognized that VEGF's suggested role in cerebral edema formation could not be proved definitively without an effective VEGF antagonist. See Kalkanis et al., 1996, *J. Neurosurg.*, 85:1095-1101 at page 1099, second column, second full paragraph.

As stated by Dr. Van Bruggen, it also could not be predicted at the time of the invention if the inhibition of VEGF by an antagonist would be sufficient to inhibit cerebral edema formation *in vivo* because of a lack of an effective antagonist that could be tested in a suitable animal model. Declaration at paragraphs 7-10. The antibody, A4.6.1, described in Ferrara could not have been used to study edema in a rodent model because it is specific for human VEGF and did not neutralize the activity of rat VEGF. This aspect of A4.6.1 prevented its use in animal model studies in which endogenously expressed VEGF is important to pathology.

Therefore, it would not have been obvious to use the VEGF antagonist disclosed by Ferrara in view of the teachings of Aiello to treat CNS edema, such as cerebral edema. There was no reasonable expectation of success that cerebral edema could be successfully treated *in vivo* with a VEGF antagonist because of contradictory evidence in the literature and lack of direct evidence of causation.

Applicants respectfully request withdrawal of the rejection on this basis.

Summary

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

Date: 21 December 2006

Eric E. DeMaster
Reg. No. 55,107

23552
PATENT TRADEMARK OFFICE